

Case Report

A Drug Toxicity Death Involving Propylhexedrine and Mitragynine*

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Abstract

A death involving abuse of propylhexedrine and mitragynine is reported. Propylhexedrine is a potent α -adrenergic sympathomimetic amine found in nasal decongestant inhalers. The decedent was found dead in his living quarters with no signs of physical trauma. Analysis of his computer showed information on kratom, a plant that contains mitragynine, which produces opium-like effects at high doses and stimulant effects at low doses, and a procedure to concentrate propylhexedrine from over-the-counter inhalers. Toxicology results revealed the presence of 1.7 mg/L propylhexedrine and 0.39 mg/L mitragynine in his blood. Both drugs, as well as acetaminophen, morphine, and promethazine, were detected in the urine. Quantitative results were achieved by gas chromatography–mass spectrometry monitoring selected ions for the propylhexedrine heptafluorobutyl derivative. Liquid chromatography–tandem mass spectrometry in multiple reactions monitoring mode was used to obtain quantitative results for mitragynine. The cause of death was ruled propylhexedrine toxicity, and the manner of death was ruled accidental. Mitragynine may have contributed as well, but as there are no published data for drug concentrations, the medical examiner did not include mitragynine toxicity in the cause of death. This is the first known publication of a case report involving propylhexedrine and mitragynine.

Introduction

Propylhexedrine is the active ingredient in over-the-counter nasal decongestants Benzedrex® and Dristan®. It is a potent α -adrenergic sympathomimetic amine that acts as a local vasoconstrictor with one-twelfth the central nervous system stimulant effects and less than one-eighth of the pressor effects of amphetamine (1). After reports of amphetamine inhalers being dismantled to extract the drug for abuse, propylhexedrine

became the active ingredient in 1949 (2). The first reported associated deaths from propylhexedrine toxicity were not reported until 1974 (3).

Propylhexedrine is abused primarily by the intravenous route, although reports of oral ingestion have been described (4). Commonly referred to as “stove top speed”, propylhexedrine can cause headache, tremor, chest pain, palpitation, rapid respiration, dilated pupils, tachycardia, myocardial infarction, psychosis, nausea, pulmonary edema, and sudden death (1,3,4–7). One publication presented 15 cases of intravenous propylhexedrine-related deaths, including 12 that died as a result of propylhexedrine intoxication. Nine of the 12 showed toxic effects with anatomical indications of right ventricular hypertrophy and pulmonary hypertension at autopsy (1).

Mitragynine is the main alkaloid found in the leaves of *Mitragyna speciosa*, a plant that is known as kratom in Thailand and biak-biak in Malaysia (8,9). Kratom contains many other indole alkaloids that are structurally related to mitragynine, including mitraphylline, speciogynine, speciociliatine, paynantheine, ajmalicine, and 7-hydroxymitragynine (10,11). Mitragynine is the major component of *Mitragyna speciosa* with a reported concentration as high as 6% by weight of the dried plant material and as much as 66% of the crude base (10,11). Mitragynine is ingested orally by chewing fresh leaves or by drinking a tea brewed with the substance (12).

Mitragynine is used for its opium-like effects at high doses. At low doses, it has stimulant-like effects similar to the coca plant. Many laborers in Asia use mitragynine to combat fatigue (10). It can also be used for opiate withdrawal, fever reduction, analgesia, diarrhea, coughing, and hypertension (8,13). Mitragynine is reported to act on the μ -opioid receptors to elicit analgesic effects (14). There are no well-defined studies to show toxicity of mitragynine. It is currently not listed as a scheduled drug in the United States. Mitragynine is not the only active compound present in *Mitragyna speciosa*; 7-hydroxymitragynine is also active and reported to have more potent analgesic effects than mitragynine. However, it is only 0.04% by weight in the plant material (11,15). Other components of the plant and some metabolites are reported to be active as well (10,13).

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Case History

The decedent, a 20-year-old Caucasian male, was found dead, under his bunk, in his living quarters. His roommate stated that it was not out of the ordinary for the decedent to sleep under his bunk. An investigation of the scene indicated no evidence of foul play. Thirty-nine separate nutritional supplements, herbal supplements, and prescription and nonprescription medications were found at the scene. Analysis of the decedent's computer and internet usage history indicated he had researched herbal supplements, particularly kratom, which he reportedly used to treat insomnia. Further investigation revealed the decedent had researched a procedure to concentrate propylhexedrine from over-the-counter inhalers. Past medical history was non-contributory to the decedent's death. Findings at the time of autopsy included bilateral pulmonary edema and bilateral pleural effusions.

Accessioning and Screening

The decedent's samples were accessioned for a standard post-mortem toxicology panel. Blood and vitreous fluid were tested for ethanol and other volatiles by headspace gas chromatography (GC). Immunoassay analysis was performed on the urine using EMIT[®], DRI[®], Abuscreen Online[®], and CEDIA[®] for drugs of abuse. A full-scan (m/z 42–550) GC–mass spectrometry (MS) basic drug screen was performed on the urine. A fluorescence polarization immunoassay (FPIA) was used to screen the urine for the presence of salicylate and acetaminophen.

Reagents and materials

All organic solvents were high-performance liquid chromatography (HPLC) grade and were purchased from Fisher Scientific (Pittsburgh, PA). Hydrochloric acid and potassium hydroxide pellets were also purchased from Fisher Scientific. Proadifen HCl, β -glucuronidase from *Helix promatia*, sodium carbonate, sodium bicarbonate, and heptafluorobutyric anhydride were purchased from Sigma Chemicals (St. Louis, MO). Formic acid was purchased from Aldrich (Milwaukee, WI). Mitragynine was purchased from ChromaDex[™] (Irvine, CA). Propylhexedrine HCl was purchased from Alltech (State College, PA). A methanolic standard of methamphetamine- d_{14} was purchased from Cerilliant (Round Rock, TX).

Standards, calibrators, and control preparation

Stock solutions of mitragynine and propylhexedrine were prepared at target concentrations of 100 mg/L and 1.0 g/L, respectively, in methanol and stored at $\leq -20^\circ\text{C}$. Stock solutions of the two internal standards, methamphetamine- d_{14} (propylhexedrine analysis) and proadifen (mitragynine analysis), were prepared in amber glass at a target concentration of 10 mg/L and refrigerated. Working solutions of mitragynine were prepared by serial dilution with methanol at concentrations of 10, 1.0, and 0.1 mg/L. Propylhexedrine working solutions were prepared similarly at concentrations of 100, 10, and 1.0 mg/L. A working solution of proadifen was prepared in deionized water at 1.0 mg/L.

Calibrators for mitragynine were spiked in certified drug-free negative blood at 0.001, 0.005, 0.010, 0.025, 0.050, and 0.10 mg/L. Calibrators for propylhexedrine were prepared in certified drug-free negative blood at 0.05, 0.20, 0.50, 1.0, and 2.0 mg/L. Positive blood controls were prepared from the same stock standard source as the calibrators because of the unavailability of multiple sources of the standards. Calibrators and controls were analyzed with each batch of samples.

Propylhexedrine sample preparation and extraction

To 2 mL of blood or urine or 2 g of tissue (homogenized) 100 μL of the stock internal standard solution for a final concentration of 0.50 mg/L, 4 drops of concentrated potassium hydroxide and 5 mL of *n*-butyl chloride were added. The samples were mixed for 20 min and centrifuged for 5 min at 3000 rpm. The upper organic layer was transferred to clean conical tubes and evaporated at 40°C under nitrogen at 5 psi after the addition of 50 μL of 10% methanolic HCl. The samples were derivatized at 70°C for 15 min using 50 μL each of ethyl acetate and heptafluorobutyric anhydride. Samples were removed from heat and evaporated at 55°C under nitrogen at 5 psi. The samples were reconstituted in 50 μL ethyl acetate, transferred to properly labeled autosampler vials, and capped.

Mitragynine sample preparation and extraction

The urine samples were hydrolyzed (1 mL of 0.1 M phosphate buffer pH 6.0, 5000 units of β -glucuronidase, 50 units of sulfatase) prior to extraction for 1.5 h at 55°C . Working internal standard solution (50 μL) for a final concentration of 0.05 mg/L and 1 mL of acetonitrile were added to 1 mL of blood or urine or 1 g of tissue (homogenized). After vortex mixing for ~ 30 s, the tubes were centrifuged at 3000 rpm for 5 min. The supernatants were poured into clean, labeled test tubes and prepared with 2 mL of 0.1 M carbonate buffer pH 9.3 and 3 mL of *n*-butyl chloride. The samples were mixed for 5 min and centrifuged for 5 min at 3000 rpm. The upper organic layer was transferred to clean conical tubes and evaporated at 55°C under nitrogen at 5 psi. The samples were reconstituted in 50 μL of 0.1% formic acid/acetonitrile (50:50, v/v).

Propylhexedrine instrumental analysis

GC–MS analysis was performed using an Agilent (Palo Alto, CA) 5890 GC coupled to a 5973 MS. The GC column was a J&W DB-5MS (20 m $\times$ 0.18-mm i.d. $\times$ 0.18 μm , Rancho Cordova, CA) with helium as the carrier gas maintained at a constant flow of 1.0 mL/min. Two-microliter split injections were made with the injector temperature held at 250°C using a 4-mm inlet liner with deactivated glass wool. An initial GC oven temperature of 70°C was held for 1 min, increased to 160°C at $15^\circ\text{C}/\text{min}$ and then to 300°C at $40^\circ\text{C}/\text{min}$ with a final hold time of 1 min; total analysis time was 11.5 min. The transfer line temperature was set at 280°C . The MS was operated in selected ion monitoring (SIM) acquisition mode. The SIM ions for propylhexedrine and methamphetamine- d_{14} were m/z 254*, 210, 182, and m/z 261*, 213, respectively (* denotes quantitation ion).

Propylhexedrine identification in the case specimens was determined by relative retention time being within $\pm 2\%$ and two ion ratios being within 20% of the averages measured from the calibrators.

Mitragynine instrumental analysis

The LC–MS–MS analysis of mitragynine was performed using an Agilent 1100 series HPLC system (Palo Alto, CA) coupled with an Applied Biosystems/MDS SCIEX 3200 QTRAP (Foster City, CA) equipped with a Turbo V™ source. Analyst 1.5 software was used for data acquisition and analysis.

Chromatographic separation was performed on an Agilent Zorbax XDB C₁₈ column (4.6 × 75 mm, 3.5 μm, Palo Alto, CA) with a Mac-Mod Analytical Halo™ C₁₈ (4.6 × 20 mm, 2.7 μm, Chadds Ford, PA) used as a guard column. The column compartment was maintained at 40°C, and the injection volume was set at 10 μL. The mobile phase was set at a constant flow of 500 μL/min and consisted of (A) 0.1% formic acid in deionized water and (B) acetonitrile. A gradient elution was used and is listed as follows: pre-injection equilibration with 70% A for 4.0 min, hold at 70% A for 1.0 min after injection, ramp to 45% A over 4.0 min, hold until 7.0 min, ramp to 35% A at 8.0 min, return A to 70% by 8.50 min, for a total run time of 8.5 min. Detailed HPLC gradient conditions are shown in Table I.

The MS was operated in positive electrospray ionization mode (+ESI). The analysis of mitragynine and proadifen (ISTD) was operated in multiple reactions monitoring (MRM) acquisition mode. Two MRM transitions were monitored for mitragynine (*m/z* 399.3/174.1* and *m/z* 399.3/226.3) and one transition for the ISTD (*m/z* 354.3/91.1*) (* denotes quantitation ion).

The source dependent parameters for the MS–MS analysis of mitragynine were determined by the flow injection analysis. Multiple injections of a 20 mg/L mitragynine standard were made, bypassing the analytical column while varying different source parameters with each sequential injection. The optimized source-dependent parameters for the analysis were as follows: GS1 gas (nebulizer) was set to 50 psi, GS2 gas (turbo) was set to 60 psi, CUR (curtain gas) was set to 25 psi, TIS (TurboIonSpray® voltage) was set to 1500 V, and the source temperature was set at 350°C.

The compound dependent parameters for the MS–MS analysis of mitragynine were determined by direct infusion. An integrated infusion pump delivered a 10 mg/L standard solution at a constant flow (10 μL/min) directly into the TIS source. The auto-optimization process determines the optimal parameters for each MRM transition. The following parameters were optimized during the process: DP (declustering potential), EP (entrance potential), CEP (collision cell entrance potential), CE (collision energy), and CXP (collision cell exit potential). Table II lists the optimal compound dependent parameter for mitragynine and internal standard.

Identification of mitragynine in the case specimens was based on the ion ratio of MRM2/MRM1 transitions being within 20% of the average ion ratios and the relative retention time being within ±2% of the averages measured from the calibrators.

Method validation

The following parameters were mea-

sured for the validation of propylhexedrine and mitragynine in human blood: selectivity, specificity, linearity, limit of quantitation (LOQ), limit of detection (LOD), upper limit of linearity (ULOL), within- and between-day precision, accuracy, and extraction recovery. Ion suppression effects were also evaluated for the LC–MS–MS method.

Selectivity was examined by extracting and analyzing six different and separate sources of negative matrices. This was done to evaluate any significant, extraneous peaks that may interfere with the analysis at the retention time of the analytes. Specificity was evaluated by analyzing positive quality control samples which contained 87 frequently encountered compounds for possible interference with the assay.

Linearity was assessed by the analysis of a multipoint calibration curve (linear regression) on separate days. The LOQ was determined by the lowest concentration which meets all the criteria for confirmation and is calculated within ±20% of the theoretical spiked mean. The LOD was determined to be the lowest concentration that meets all the criteria for confirmation but the calculated concentration is greater than ±20% of the theoretical spiked mean. The ULOL was determined by the highest concentration which meets all the criteria for confirmation and the calculated concentration was within ±20% of the theoretical spiked mean.

Within-day precision was measured by the analysis of five aliquots of three controls at different concentrations in a single extraction. Between-day precision was measured with the analysis of one aliquot of three controls over five separate extractions. The acceptable value of precision, expressed as the coefficient of variation (CV), for each within-day and between-day assays must be < 15%. Accuracy, defined as percent difference from the theoretical spiked concentration (% diff), was determined for each of the three controls over

Table I. Gradient Elution Timetable*

Step	Time (min)	Flow Rate (μL/min)	%A	%B
0	4.0	500	70	30
1	1.0	500	70	30
2	4.0	500	45	55
3	7.0	500	45	55
4	8.0	500	35	65
5	8.5	500	70	30

* (A) 0.1% formic acid in deionized water; (B) acetonitrile.

Table II. Optimal Compound-Dependent MS–MS Parameters

Compound	MRM Transition (<i>m/z</i> / <i>m/z</i>)	Compound-Dependent Parameter				
		DP	EP	CEP	CE	CXP
Mitragynine	399.3/174.1	60.0	4.0	25.0	40.0	4.0
	399.3/226.3	60.0	6.0	25.0	35.0	2.0
Proadifen (ISTD)	354.3/91.1	37.0	10.0	24.0	50.0	3.0

each extraction. Each control concentration within $\pm 20\%$ of the theoretical spiked concentration was considered acceptable.

Extraction recovery studies were performed by comparing unextracted standards to extracted blood samples where the drug was added post- and pre-extraction. The study was performed at several different concentrations over the linear range. The extraction recovery was calculated as the difference between the samples where the standards were added post-extraction versus pre-extraction. The ion suppression or enhancement was determined to be the signal difference, positive or negative, between the extracted blank matrix, the mobile phase, and the unextracted infused mitragynine standard.

Results

Method validation

The validation data met all acceptable criteria for method validation. No interferences, excessive background, or endogenous peaks were detected in six separate sources of negative blood and urine. No extraneous interfering peaks or ions were detected from the quality control samples containing 87

frequently encountered compounds for propylhexedrine or mitragynine. No significant ion suppression or enhancement was detected with either matrices (blood and urine) or the mobile phase. The precision, accuracy, and linearity all meet the acceptable criteria for validation. The validation data, including linearity, LOQ, LOD, ULOL, precision, accuracy, and extraction recovery, are summarized in Table III.

Case results

No ethanol (cutoff 0.02 g/dL) or other volatile substances (cutoff 0.001 g/dL) were detected in the decedent's blood and vitreous fluid. Urine immunoassay screening produced positive results for the Roche (Indianapolis, IN) Abuscreen Online Amphetamines and Opiates assays. Confirmation testing for amphetamines failed to identify amphetamine, methamphetamine, phenylpropanolamine, pseudoephedrine, ephedrine, methylenedioxymphetamine, and methylenedioxymethamphetamine at an LOQ of 0.05 mg/L in urine. Opiate confirmation testing showed presence of morphine in the urine, not in the blood and negative for codeine, hydrocodone, hydromorphone, oxycodone, and oxymorphone at an LOQ of 0.05 mg/L for blood and urine. 6-Acetylmorphine was negative by immunoassay at a 10 ng/mL cutoff. A full-scan GC-MS base screen detected promethazine, propylhexedrine, and mitragynine in his urine. The FPIA for acetaminophen was positive in the urine and confirmed by color test. No other therapeutic or abused drugs were detected. Table IV provides quantitative results in the blood; Table V represents the tissue distribution for propylhexedrine and mitragynine in specimens received.

Table III. Method Validation Data for Propylhexedrine and Mitragynine in Blood

	Mitragynine		Propylhexedrine	
Linearity ($n = 8$)	0.001–0.100 (mg/L)		0.05–2.0 (mg/L)	
r^2	> 0.9951		> 0.9973	
LOD (mg/L)	0.00025		0.02	
LOQ (mg/L)	0.001		0.05	
ULOL (mg/L)	0.100		2.0	
Recovery ($n = 4$)	103%		94.2%	
Precision[†]	SD*	CV[†]	SD*	CV[†]
Within-day ($n = 5$)				
low control	0.26	8.9%	0.02	5.1%
mid control	0.63	4.0%	0.02	2.2%
high control	8.15	10.7%	0.05	3.1%
Between-day ($n = 5$)				
low control	0.08	3.0%	0.01	4.6%
mid control	0.86	5.7%	0.04	4.2%
high control	3.56	4.6%	0.12	7.2%
Accuracy[‡]	% diff		% diff	
Within-day ($n = 5$)				
low control	15.2%		16.0%	
mid control	4.7%		8.0%	
high control	1.2%		6.0%	
Between-day ($n = 5$)				
low control	11.8%		8.0%	
mid control	0.8%		6.7%	
high control	3.0%		4.7%	

* Standard deviation.

[†] Defined as the [(standard deviation/mean)*100].

[‡] Controls for mitragynine are 2.5, 15.0, and 75.0 ng/mL. Controls for propylhexedrine are 0.25, 0.75, 1.5 mg/L.

Table IV. Blood Quantitation Results

Drug	Concentration (mg/L)
Propylhexedrine	1.74
Mitragynine	0.39
Morphine	< 0.05
Promethazine	< 0.05
Acetaminophen	< 5.0

Table V. Propylhexedrine and Mitragynine Tissue Distribution

Source	Propylhexedrine	Mitragynine
Heart blood (mg/L)	1.74	0.39
Urine (mg/L)	51.96	1.20
Liver (mg/kg)	16.29	0.12
Vitreous humor (mg/L)	1.96	0.15
Kidney (mg/kg)	11.25	0.16
Heart (mg/kg)	5.48	None detected
Spleen (mg/kg)	7.78	0.18
Lung (mg/kg)	7.37	0.01
Bile (mg/L)	11.31	0.48

Discussion

The propylhexedrine blood and tissue concentrations were in range of previously reported deaths caused by propylhexedrine (1,3,4,7). The autopsy findings of bilateral pulmonary edema are also consistent with other reports for propylhexedrine toxicity deaths. The combination of mitragynine with propylhexedrine may have added to the toxicity of each drug. A published report of a patient admitted to the hospital for generalized tonic-clonic seizures was taking mitragynine and modafinil (16). The patient had been ingesting kratom tea for 3.5 years prior to

this episode. He took 100 mg of modafinil to improve his alertness, and 20 min later, he went into a seizure. Modafinil is a α -adrenergic agonist and CNS stimulant similar to propylhexedrine (5). It is used as a “go-pill” in the military for pilots.

Despite the specificity generally associated with LC-MS-MS analysis, the analysis of the decedent's blood and urine specimens for mitragynine produced four co-eluting peaks sharing the same $[M + 1]$ of m/z 399, MRM transition, and MRM ratios. Figure 1 displays the total ion chromatogram and the product ion scans for each of the indole alkaloids and metabolites identified in the decedent's urine. As noted previously, *Mitragyna speciosa*, or “kratom”, contains many in-

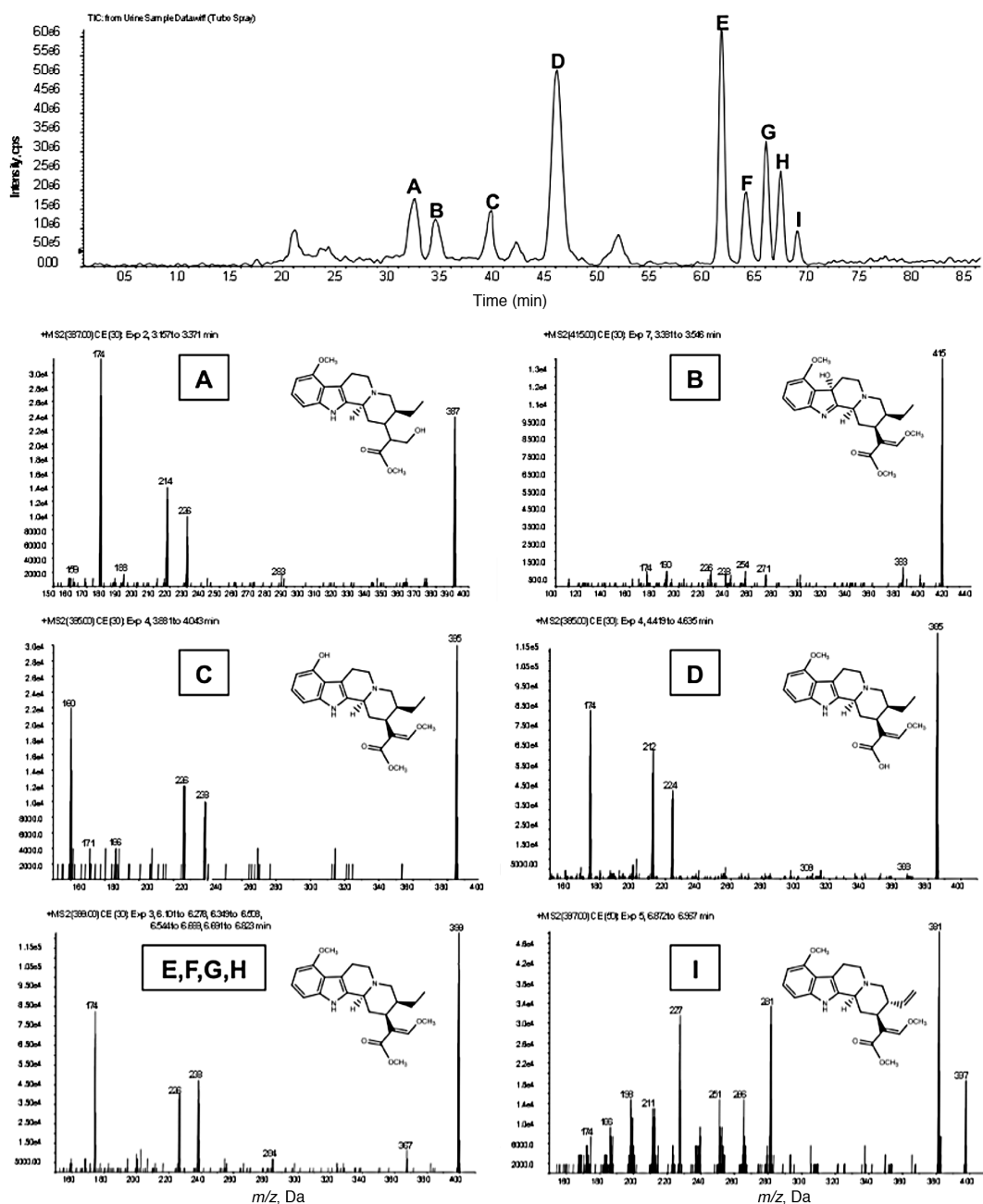


Figure 1. Total ion chromatogram of the decedent's urine including product ion scans for 17-O-desmethyldihydromitragynine (A), 7-hydroxymitragynine (B), 9-O-desmethylnitragynine (C), 16-carboxymitragynine (D), mitragynine (E), speciogynine (F), speciociliatine (G), unidentified peak (H), and paynantheine (I).

dole alkaloids structurally related to mitragynine, including mitraphylline, speciogynine, speciociliatine, paynantheine, ajmalicine, and 7-hydroxymitragynine (10,11). The LC method was improved to separate all the co-eluting peaks in both the blood and urine. Two of the three peaks containing $[M + 1]$ of m/z 399 are most likely the structural isomers of mitragynine; speciogynine and speciociliatine. The third peak containing $[M + 1]$ of m/z 399 was also observed by Kikura-Hanajiri et al. (11) in dried plant material but remains unidentified. Because of the many chemicals used during the processing of the plant material and the extraction of the biological sample, it is not certain that this third unidentified compound with $[M + 1]$ of m/z 399 is naturally occurring or an artifact made during one of these processes. The possibility that it is a metabolite is unlikely because of the work reported by Kikura-Hanajiri et al. (11). However, it could be possible that it is some type of breakdown product formed during drying. A fourth peak was observed with an $[M+1]$ of m/z 397, which corresponded to an endogenous compound (paynantheine) previously identified in *Mitragyna speciosa* (10,11). Additional analysis of the decedent's urine using LC-MS-MS ion product scan revealed the presence of a number of metabolites including 16-carboxymitragynine, 9-*O*-desmethylnitragynine, and 17-*O*-desmethyldehydromitragynine. Although no standards were available, tentative identification was made based on the MS m/z profiles of each metabolite using the published metabolic studies performed by Philipp et al. (13,17).

The tissue distribution of propylhexedrine and mitragynine indicate both similarities and differences. Both drugs distribute into vitreous humor in concentrations on the same order as blood. Bile and urine are useful screening specimens for both drugs. Although both drugs distribute widely throughout the central tissues, the extent of distribution is different. Mitragynine distribution into the liver, kidney, and spleen is of the same order of magnitude as the blood concentration, whereas propylhexedrine concentrations in the liver, kidney, and spleen are approximately an order of magnitude higher than the blood.

Conclusions

Two validated methods were used to analyze propylhexedrine and mitragynine in the presented case. Two different methodologies were implemented: GC-MS and LC-MS-MS. LC-MS-MS was chosen to analyze mitragynine to allow for additional identification of other compounds present in the plant as well as metabolites of mitragynine. This is the first published case report involving the co-ingestion of propylhexedrine and mitragynine. No case reports of propylhexedrine toxicity have been reported in over 20 years. The cause of death was ruled propylhexedrine toxicity and the manner of death was ruled accidental. Mitragynine may have contributed as well, but because there are no published data on drug concentrations, the medical examiner did not include mitragynine toxicity in the cause of death.

Acknowledgments

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